Applications of high throughput screening to identify profiles of biological activity relevant to carcinogenesis

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ToxCast, the United States Environmental Protection Agency's chemical prioritization research program, is developing methods for utilizing computational chemistry and bioactivity profiling to predict potential for toxicity and prioritize limited testing resources (www.epa.gov/tocast). This presentation will provide an overview of the rationale, design and status of ToxCast. In Phase I, our proof-of-concept component, we have focused upon evaluating chemicals with an existing, rich toxicological database in order to provide an interpretive context for the high through put screening data. This set of 320 reference chemicals, largely food use pesticides, and represents numerous structural classes and phenotypic outcomes. The in vivo datasets include standard chronic bioassays in the rat and the mouse. Bioactivity data is derived from a broad spectrum of more than 500 readouts from biochemical assays, cell-based phenotypic assays, and model organisms. Of particular note are a number of assays exploring the function of nuclear receptors (e.g., ER, AR, CAR, PXR, PPAR, AhR, LXR, RAR) potentially involved in non genotoxic carcinogenesis. Correlations of ToxCast data with rodent tumor formation will be presented. ToxCast is part of a larger government effort (Tox21) being conducted jointly by EPA, the National Toxicology Program of NIEHS, and the NCGC that is obtaining high throughput screening data on more than 2000 chemicals, with plans to expand to nearly 10000 chemicals in 2009. *This is an abstract of a proposed presentation.*